Cystic Fibrosis Corrected in Lab

Two teams of investigators have used gene transfer to correct the cystic fibrosis defect in cells in culture, opening the door, at least a crack, for gene therapy.

"We are talking about years, not decades any longer," says a clearly elated Robert Beall, vice president and medical director of the Cystic Fibrosis Foundation. "We hope this will move CF up the list of diseases that are candidates for gene therapy." Cystic fibrosis is the most common fatal genetic disease in North America.

Announcement of these results follows by just 1 week the first attempt at human gene therapy—an experiment at the National Institutes of Health that Beall believes goes far toward removing some of the social and ethical obstacles to this strategy, if not the scientific ones.

"There are tremendous hurdles to overcome, but this means that at least we ought to run the race. It suggests it might be realistic to think about gene therapy," says Michael Welsh, a Howard Hughes Medical Institute investigator at the University of Iowa, who led one team along with Alan Smith of Genzyme Corporation of Framingham, Massachusetts, and Douglas Jefferson of Tufts University. Their work will be published in the 27 September issue of *Nature*.

The other team was led by Hughes investigators James Wilson and Francis Collins of the University of Michigan and Raymond Frizzel of the University of Alabama, Birmingham. Collins was part of the team that discovered the cystic fibrosis gene last year. The Michigan group's paper was published in the 21 September issue of *Cell*.

Although the two teams took different tacks to insert the normal gene into the defective cells, both achieved essentially the same result: they opened up the chloride channel that is plugged in cystic fibrosis. Because of the closed channel, chloride cannot exit and water is pulled into the cell, leading to the buildup of thick, dry mucus in the lungs that is characteristic of the disease.

The Michigan group used a retrovirus to ferry the gene into a pancreatic cancer cell line derived from a cystic fibrosis patient. The gene was stably inserted into the chromosome and began churning out its protein product, known as cystic fibrosis transmembrane conductance regulator, or CFTR, which then stimulated the channel to open. The Iowa team used a modified vaccina virus to insert the gene into airway epithelial cells.

Stunning as these achievements are, translating them into clinical practice won't be easy. First of all, the investigators have to show that the normal gene can be expressed in vivo. They also need an animal model, which four groups are racing to produce; Beall expects success within a year. Then they must ascertain whether opening the chloride channel actually prevents mucus buildup, as they assume it will.

Perhaps the biggest obstacle is delivery: "how to get the vector into the airways of a living, breathing person—and do it safely," says Collins. Not only must they get the healthy gene to the right cells, but they must get it there in sufficient quantity to correct enough cells for the airway to begin functioning normally. "That is not a trivial problem," says Collins.

The ideal strategy would be to target the progenitor cells that give rise to the airway cells affected in cystic fibrosis. But unfortunately, says Beall, "we don't know the origin of the cells that are affected."

So, as a sort of interim form of gene therapy, the investigators envision an aerosol containing the normal gene in a suitable vector, which a patient would inhale. It might be possible to get enough of the normal gene into airway cells this way, but the therapy would have to be repeated periodically as these transformed cells die off.

Meanwhile, these new studies have provided indisputable proof that the gene discovered a year ago is in fact the cystic fibrosis gene, says Beall. The new work should also speed efforts to figure out exactly what CFTR does. Some people now think CFTR pumps another compound in and out of the cells, and that the second, yet unknown compound regulates chloride ion transport. "I think we don't know and we need to find out," says Welsh.

Cystic Fibrosis Foundation

Upbeat prognosis: *"We're talking about years, not decades," says Robert Beall.*

Both teams have managed to grow great quantities of CFTR for the first time. And Alan Smith of the Iowa team has now produced antibodies to CFTR in rabbits. Because these antibodies bind to CFTR, they can show exactly where the protein functions in the cell. And once investigators figure out what goes wrong with CFTR in cystic fibrosis, they may be able to design pharmacological strategies to combat the disease. Says Walsh: "We may even find a drug that is better than gene therapy."

■ LESLIE ROBERTS

Partner Found for the Myc Protein

Earlier this month, at the Cold Spring Harbor Laboratory's symposium on the "Origins of Human Cancer," Robert Eisenman of the Fred Hutchinson Cancer Research Center in Seattle scrapped his scheduled talk to describe an intriguing new result from his lab: His group has identified a protein that may provide some long-sought answers to how the *myc* oncogene works.

The *myc* gene is one of the best studied of all oncogenes. And for good reason: A great deal of evidence indicates that alterations in the gene can contribute to the development of a wide range of cancers, including common malignancies such as lung cancers, as well as relatively rare ones, such as Burkitt's lymphoma.

Yet, despite the vast amount of work on *myc*—a Medline search by Eisenman turned up 2700 papers on the gene since the 1970s—researchers haven't been able to figure out exactly what the protein encoded by the *myc* gene does normally in the cell or how it malfunctions in cancer cells. "We have accumulated a lot of interesting facts about the *myc* protein," Eisenman says, "but they don't tell us what the heck is going on." The new protein identified by Eisenman's group may change that, for it appears to be a missing link in the *myc* protein's chain of actions.

myc mavens have long suspected that the protein encoded by their favorite oncogene regulates gene expression. The "interesting facts" accumulated over the years include the finding that the *myc* protein is located in the nucleus, the expected location for a gene regulator. Moreover, the protein sequence includes two structural motifs—a "helix-loop-helix" and a "leucine zipper"—found in certain proteins known to regulate gene activity. Generally two or more of these proteins have to act in concert, and the helix-loop-helix and leucine zipper structures serve

to bring the partners together. Their joining forms the binding site that enables the protein complex to attach to specific DNA sequences on the genes it regulates.

Researchers have been stymied, however, in their efforts to identify the genes that the *myc* protein might regulate because they were unable to find either a protein partner for it or the specific DNA sequences to which it binds. That's the problem the Eisenman group now appears to have solved.

The *myc* protein may have been so hard to study, Eisenman says, because the isolated molecules have a strong tendency to interact with each other, forming aggregates that preclude their interacting with other proteins or with DNA. The Seattle workers got around this problem by using a 92–amino acid segment of the protein containing the helix-loop-helix and leucine zipper motifs instead of the whole protein. Keith Blackwell, who works in Harold Weintraub's lab at the Hutchinson Cancer Center, was then able to identify a specific DNA segment to which that sequence binds. But the binding was weak, Eisenman says, which is an indication that another protein cooperates with the *myc* protein to form a DNA recognition site.

So the next step, undertaken by Elizabeth Blackwood, a graduate student in Eisenman's lab, was to find that protein. She again used the 92–amino acid *myc* segment, this time to screen a library of protein-producing mammalian DNA clones. It was a tedious task. Out of 1 million clones screened, she found just two producing a protein that bound to the *myc* protein segment. Both turned out to be producing the same protein, and the Eisenman group has now sequenced the corresponding DNA clone. The protein encoded by the gene, which the researchers are calling *max* (for *myc*-associated X), is a new one; the sequence does not appear in any of the data banks. It bears a partial resemblance to the *myc* protein, however, especially in the helix-loop-helix and leucine zipper regions. "That's exactly what you would expect for something that would bind the *myc* protein," Eisenman says. "We think it's possible that we have finally found a binding partner for it."

Participants in the Cold Spring Harbor meeting were enthusiastic about the work because it opens the door to identifying the genes regulated by the *myc* protein and dissecting its normal and pathological roles in the cell. But the work may have a wider significance as well. The method used for finding *max* may also be useful for identifying the binding partners of other gene regulatory proteins, thereby leading to a better understanding of gene control generally. ■ JEAN MARX

Millimeter Astronomers Push for New Telescope

The new facility would give them an unprecedented ability to study star and galaxy formation—but at a cost of $120 million

IN AN ERA OF GRAMM-RUDMAN BUDGET cuts, shrinking research grants, and post-Hubble sensitivities, it takes more than a little chutzpah to propose yet another big science project, especially one in a relatively new field. But that is what a stalwart band of astronomers, led by Robert Brown of the National Radio Astronomy Observatory, has just done. Their plan—to build a complex new telescope for detecting millimeter-wavelength radiation—landed on the desk of Laura Bautz, director of the National Science Foundation's astronomy division earlier this month. All they're asking for is a cool $120 million. That would make their scope, known as the Millimeter Array, the most expensive ground-based astronomical facility yet constructed.

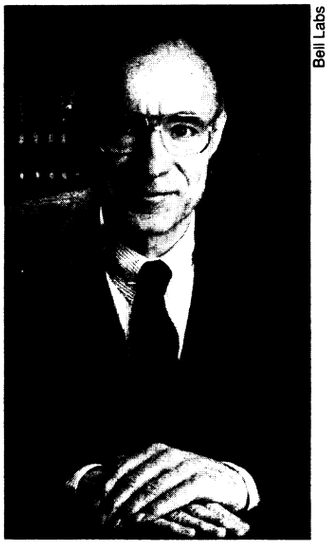
It would be worth every penny, maintains Brown. "Millimeter astronomy tells you about interstellar gas clouds—where they are, what they're made of, and what they're doing," he says. "And since what they spend a lot of time doing is making stars and galaxies, millimeter astronomy provides you with important clues about the birth and evolution of the universe."

Since other forms of astronomy can't provide that kind of information, millimeter astronomy has soared in stature since it burst onto the scene a mere 20 years ago. Before then, the researchers had known little about the existence, composition, location, and behavior of interstellar clouds, which are invisible at most wavelengths. What they did know came through the centimeter "window" onto the electromagnetic spectrum, which was partly opened in 1951 when Harvard astronomers Edward Purcell and Harold Ewen detected the 21-centimeter spectral line emitted by atomic hydrogen with an antenna protruding from the Lyman Laboratory.

By the mid-1960s, when centimeter astronomy was in its heyday, researchers were laboriously mapping the clouds' hydrogen distribution. Their objective was to assemble supposedly complete radio maps of interstellar gas clouds, which were then published in the *Astrophysical Journal*. But they little suspected that a revolution that would improve the resolution of the maps by orders of magnitude was just around the corner.

At the time, millimeter astronomy was not in high repute. During the 1960s, the National Radio Astronomy Observatory (NRAO), which is headquartered in Charlottesville, Virginia, had built a 36-foot telescope in the millimeter range on Kitt Peak in Arizona. One goal was to use the facility to detect the continuum radiation created by such things as supernovas and radio galaxies. But the telescope, which was completed in 1967, proved to be a disappointment—at first. It had been troublesome to build, it never reached its design specs for accuracy, and it turned out to be difficult to use.

Most frustrating of all, at the outset there was little scientific payoff. The continuum sources were unexpectedly weak, and their study failed to yield the surprises usually turned in by a major new instrument. Things were so disappointing that for several years the Kitt Peak telescope was unique among U.S. telescopes in that it was easy to get time on.



Bell Labs

Millimeter astronomy pioneer. *Arno Penzias saw a new window into space to exploit.*

But that was before Bell Labs scientist Arno Penzias entered the picture. In the late 1960s, Penzias was impressed by recent discoveries of certain interstellar molecules. They had been newly observed through the centimeter window by means of the spectral bands related to the low-energy quantum transitions that result when molecules are stretched, bent, or rotated. He began to suspect that the millimeter region—in which the bulk of such transitions occur—harbored vast potential as an